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Original Article

Spectrum of Infections in Children with Newly Diagnosed Primary Nephrotic Syndrome

Khemchand N Moorani, **Mukesh Raj**
Department of Pediatric Nephrology, National Institute of Child Health, Karachi.

Abstract

Background: Children with primary nephrotic syndrome are more susceptible to bacterial infections which may trigger disease or relapse or cause steroid resistance in these children.
Objectives: To determine the spectrum of infections in children with newly diagnosed primary nephrotic syndrome.
Study type, settings and duration: A Retrospective case record analysis was carried out in the department of Pediatric Nephrology, National institute of child health (NICH), Karachi from January 2007 -December 2008.
Subjects and Methods: Patients with newly diagnosed primary nephrotic syndrome who presented with various bacterial infections were included in the study. Data for age, gender, type of infection were computed on SPSS -10 and analyzed using descriptive statistics.
Results: A total of 355 children with renal problems were registered during the study period, out of which 155 were newly diagnosed primary nephrotic syndrome. Sixty (38.7%) children had one or more infections at the time of admission. There were 34(56.7%) boys and 26(43.3%) girls whose ages ranged from 1-15 years (mean 5.22 years). Majority of patients (36) were below 5 years of age and 24(40%) were above 5 years. Acute respiratory tract infection and urinary tract infections were the most common infections found in 28(46.6%) and 15(25%) cases respectively. Common clinical presentation was edema (100%) followed by fever in 52(86.6%), cough in 28(46.6%), urinary symptoms in 12(20%), vomiting in 8(13%) and diarrhea in 7(11.6%).One patient presented with convulsions.
Conclusions: For children presenting with primary nephrotic syndrome, acute respiratory infection and urinary tract infections should be kept as the commonest reason for infection.
Policy message: Training of paediatricians is required in diagnosing these chronic illnesses.
Key words: Respiratory tract infection, urinary tract infection, peritonitis.

Introduction

Primary nephrotic syndrome (PNS) is a common renal disorder in the pediatric age group and minimal change disease (MCD) is the most common underlying histopathological lesion (80–90%). Majority of children with MCD are steroid sensitive and long term prognosis is benign.[1] However, 40-50% show frequent relapses and a prolonged course of illness may pose children at risk of life threatening infections, thromboembolic complications and side effects of therapy.[1-3] Focal segmental glomerulosclerosis, mesangial proliferative and membranoproliferative glomerulonephritis are the other histopathological types, usually associated with steroid resistance.[2-4]

Infection is an important cause of morbidity and mortality in nephrotic children especially in developing countries.[5-8] Children with PNS have increased susceptibility to bacterial infections and various infections may result in relapses or steroid resistance or may trigger the onset of disease.[2,5-7] Relapses in steroid sensitive nephrotic syndrome often follow infections of upper airway or gastrointestinal tract. It is estimated that 52–70% of relapses among children in developing countries chiefly follow the upper respiratory tract infection.[6,7] Common infections associated with either onset of disease or during the course of disease are acute upper and lower respiratory infections (ARI) including pneumonia with or without empyema, skin infections including impetigo and cellulitis, acute gastroenteritis (watery diarrhea) or dysentery, urinary tract infections (UTI) and primary peritonitis.[6-11]

Studies have shown that use of prophylactic antibiotics, immunoglobulins replacement therapy, vaccination against *streptococci pneumoniae*, thymosin as immuno-modulating agent, use of Chinese medicinal herb (Tiaojining) and zinc supplements may have a role in prevention of these infections.[12-16] However, in a recent Cochrane Database of Systemic Review, it has been concluded that there is no strong evidence for any

Corresponding Author:
Khemchand N Moorani
Department of Pediatric Nephrology
National Institute of Child Health
Karachi.
Email: khemchandn@hotmail.com

intervention for prevention of infection in nephrotic syndrome.[17]

Though pneumococcal peritonitis and cellulitis are decreased with use of pneumococcal vaccine and wide spread use of antibiotics but these infectious complications / septicemias may still be responsible for 1.4-10% of mortality in these children.[7,8] In addition infections may also be responsible for repeated relapses requiring high dose of steroids and hospitalization.[5,9]

A high frequency of infections in children with nephrotic syndrome has been reported from developing countries like India, Pakistan & Bangladesh. The frequency of infections that ranges from 38% to 83% seen in these studies.[6-11]

Studies from developing countries have also suggested that increasing the maintenance of daily dose of steroid from alternate day dose in a child with remission during the episode of mild infections can prevent relapse.[18,19]

Thus a strong suspicion regarding infections in a nephrotic child is important not only for the treatment to decrease morbidity and mortality but also to prevent infection associated relapse.

Multiple factors contribute to increased susceptibility to bacterial infections. These include decreased immunoglobulin (IgG) levels due to impaired synthesis and urinary loss, edema fluid acting as a culture medium, protein deficiency especially low serum albumin, hypovolemia leading to decrease perfusion of spleen, loss of complement factor B and D required for phagocytosis of encapsulated organisms, impaired T-lymphocyte function and effects of immunosuppressive therapy commonly used in these children.[20-22]

In Pakistan, about 5-9% of hospital admissions are due to various kidney diseases and nephrotic syndrome is the most common accounting for 50% of all renal cases.[5] Certain studies on this important aspect of infections in nephrotic syndrome have been carried out in Pakistan, such as frequency and types of infections in children with nephrotic syndrome.[5,7,8] But these studies included all types of children with nephrotic syndrome who were either steroid resistant, dependant or frequent relapsers. In these groups immunosuppressive therapy may have contributed for high prevalence of infection. The literature does not show a single study which had shown infections in newly diagnosed primary nephrotic syndrome. All studies so for done on infectious complications have included primary nephrotic syndrome who were either on steroid therapy or treated with steroids in their course of illness.[6-8]

So, this study was carried out to determine the spectrum of various infections in newly diagnosed nephritic syndrome patients. This may help in developing guidelines for primary physicians and pediatricians on preventive strategies, diagnostic workup and therapeutic measures regarding infections in steroid sensitive nephrotic syndrome which may be of help in prevention of relapses.

Subjects and Methods

It was a retrospective case series study carried out in the department of Pediatric Nephrology, National institute of child health (NICH), Karachi from January 2007-December 2008.

Children of 1-15 years of age who had developed nephrotic syndrome for the first time and fulfilled the International Study of Kidney Disease in Children (ISKDC)[1] criteria for diagnosis of primary nephrotic syndrome (PNS) were enrolled in the study through OPD, nephrology ward and emergency room. The diagnosis of PNS was made on the basis of presence of generalized edema, heavy proteinuria $\geq$40 mg/m^2/hr, hypoalbuminemia $\leq$2.5 gm/dl and hypercholesterolemia $\geq$250 mg/dl. Children with known PNS presenting with relapse or already on steroid therapy and on antibiotic treatment were excluded and those having congenital and secondary nephrotic syndrome.

All patients underwent history, physical examination and relevant laboratory investigations i.e. spot urine albumin, urinary protein/creatinine ratio or 24 hour urinary protein, complete blood count, urine analysis, serum protein, serum albumin and serum cholesterol.

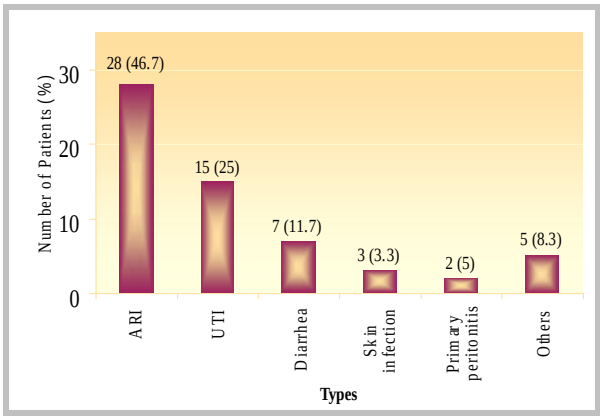
To establish the diagnosis of infections, all children were evaluated clinically and screened for evidence of infections using urine, blood, CSF, peritoneal fluid culture and sensitivity, chest X-rays PA view (in selected cases), stool detailed report and skin swab for C/S where necessary.

Data including age, gender, type of infection were computed and statistical analysis was performed by SPSS version 10. Descriptive statistics, frequency and percentages were calculated to present all categorical variables including sex, age groups, type of infections, clinical features and laboratory parameters. Age was presented as Mean$\pm$SD.

Results

A total of 355 children with renal problems were registered during the study period. Out of these 155(43.7%) were newly diagnosed primary nephrotic syndrome cases and 60(38.7%) had evidence of infection and thus fulfilled the inclusion criteria of study. Other 95 patients were excluded as they did not have infection. There were 34(56.6%) boys and 26(43.3%) girls with male to female ratio of 1.3:1. Their ages ranged from 1-15 years (mean of 5.2$\pm$3.1 years). In age group $\leq$5 years, there was no gender difference; however, there was slight male preponderance (66.7%) in over 5 years age group.

Most common infections were acute respiratory tract infection found in 28(46.6%) and this included both upper and lower ARI followed by urinary tract infection (UTI) in 15(25%) cases, diarrhea in 7(11.7%) and skin infection in 3(5%) cases (Figure). In 28 patients with ARI, 20(71.4%) had lower respiratory tract involvement confirmed as pneumonia while 8(28.6%) had upper respiratory infection.



ARI = Acute Respiratory tract Infection, UTI = Urinary Tract Infections
Others = each one (1.7%) with Enteric fever, Pulmonary TB, Meningitis, Chicken pox, Sepsis.

Figure: Types of infections in newly diagnosed primary nephrotic syndrome.

Table-1 shows the clinical presentation in newly diagnosed PNS. Edema was present in all 60 patients and its severity ranged from mild puffiness of face or pedal edema to generalized edema associated with ascites and scrotal or labial edema. Fever, cough and urinary symptoms were the most common presentations observed in 52(86.6%), 28(46%) and 12(20%) cases respectively. One patient presented with convulsion and was diagnosed to have bacterial meningitis.

Table 1: Clinical presentations of children with infections in newly diagnosed primary nephrotic syndrome. (N=60)

Presentation	*Frequency*	*%*
Edema	60	100
• Generalized	39	65
• Abdominal wall	10	16.7
• Ascites	06	10
• Scrotal edema	05	8.3
Fever	52	86.7
Cough	28	46.7
Urinary symptoms	12	20
Vomiting	08	13.3
Diarrhea	07	11.7
Abdominal pain	04	6.7
Dehydration	02	3. 3
Skin infection	03	05

Three patients presented with localized skin infections (abscess on leg in 2 and cellulitis over anterior abdominal wall in 1).

Leucocytosis was seen in 17(60.7%) cases having lower respiratory tract infection while consolidation or patchy infiltrations were seen on chest X- rays in 12(42.9%) patients. Throat culture was positive in 2 cases which grew *streptococcus pneumonae.*

Of the 15 cases with UTI, urine microscopy and culture showed growth in 13(86.6%) cases and 12(80%) of these cases were symptomatic. *E. Coli* growth was observed in 69.2% specimens (Table-2). Primary peritonitis was seen in 2(3.3%) cases who presented with typical abdominal pain, vomiting and fever. Peritoneal fluid was exudative in both of them but gram staining and cultures were negative.

Table 2: Urinary tract infections. (N=15)

UTI	*Number of Patients*	*%*
Urinary symptoms	12	80
Positive urine culture	13	86.7
Negative urine culture	02	13.3
ORGANISMS		
• *E.Coli*	09	69.2
• *Klebsella*	03	23.1
• *Proteus*	01	7.7

Discussion

Urinary tract infection and respiratory infections are the commonest causes of infection in children with primary nephrotic syndrome. Nephrotic syndrome in children is an immuno-compromised state due to hypoproteinemia particularly hypogammaglobulinemia (urinary loss and impaired synthesis of IgG,), decreased complement factor B (C_3 proactivator) and D, both being essentials for phagocytosis of encapsulated pathogens.[2,3,14,20,22] Furthermore, there is also evidence of abnormal T-lymphocyte function, hypovolemia resulting in hypo-perfusion of spleen and intestinal mucosa leading to hyper-coagulation and micro-infarcts, edematous tissue providing culture medium for bacterial growth. Immunosuppressive effects of therapy may also contribute to this immuno-compromised state.[17] The current recommended strategy for the prevention of relapses associated with infections in developing countries is to increase the dose of daily steroid for a short period of time during the episode of inter-current infection.[18-19]

Many studies have shown the preventive role of various strategies in children with nephrotic syndrome such as use of prophylactic antibiotics, immunoglobulins replacement therapy and vaccination against *Streptococci* pneumonia; thymosin as immunomodulating and T cell

stimulating agent, use of Chinese medicinal herb (Tiaojining) and zinc supplements.[12-16]

Infections are responsible for high morbidity and mortality due to severe infections such as pneumonia, primary peritonitis and septicemia leading to multi organ failure.[6,7,14,23] The milder forms of infections like upper ARI, diarrhea and urinary tract infections may be responsible for exacerbation of proteinuria and recurrent relapses of nephrotic syndrome.[9,11] These infections are also the main reasons for hospitalization along with delayed response to steroid or discontinuation of steroid therapy in some cases.[1,2,6-8,] In the present study the mean age of study population was 5.2 years and majority (60%) were below 5 years. Since the present study consisted of all new cases of nephrotic syndrome , so this mean age of 5 years represents the age of onset of nephrotic syndrome in our population. This is similar to reported figures from previous Pakistani studies and from the West.[2,3,5-7]

The spectrum of infections in this study showed that ARI was the most common type of infection (46%) followed by UTI (25%) and diarrhea (11%). The spectrum of infection in the present study is different from our previously published study.[7] The present study shows that the frequency of ARI has increased from 30% to 46%, but the frequency of lower ARI is almost similar 72.7% as reported by us previously.[7] All patients with ARI in the current study had active disease which is similar to as reported in our previous study in which more than 80% cases had active nephrotic state.[7] This is also similar to another local study and a report from neighboring country.[6-9] The higher frequency of lower ARI (pneumonia) in nephrotic children may be due to lack of localization of infection and mechanical pressure on lungs due to massive ascites and pleural effusions leading to stasis of fluid in the lungs in these children.[2]

Urinary tract infections (UTI) emerged as the second most common infection accounting for 25% of cases in the current study. In our previous study UTI stood as fourth most common after skin infections (27%) and diarrhea (13.5%).[7] A high prevalence (66.7%) of UTI has recently been documented in two studies from Africa.[24,25] Similar high prevalence of UTI has also been reported in studies from India where its frequency ranged from 22.8 % to 46%.[6,9,10] *E. Coli* in most studies is still as the most common pathogen of the UTI.[6-10]

Third most common infection was diarrhea and similar frequency is reported in other studies from Pakistan showing that there is no effect of immunosuppressive therapy for repetitive relapses associated with diahorea.[7,8] Similar frequency of diarrhea (10.5%) has been reported from India. Other two studies from the same country show different results.[6,9] This variation might be due to variation in the definition of diarrhea since it is also taken as part of presentation of nephrotic syndrome due to gut edema.

Skin infections are known to be associated with onset of disease or active disease state but the frequency in this study has decreased from 27.7% reported in our previous study to 5% in the current study. The frequency of cellulitis in the present study was similar to 3.8% in one study but higher figures were reported in another study.[8,10]

Primary peritonitis was seen in 3.3% cases in the present study and this is lower than 10%, 15.7% and 28.8% reported by others.[6,7,21] Low figure (2.9%) of primary peritonitis has been reported in a 5 year multicenter study from Europe in which 8 episodes were observed among 268 children with steroid sensitive nephrotic syndrome.[23] This low prevalence of primary peritonitis may reflect the effects of pneumococcal vaccine or frequent use of early antibiotics as recommended by various authorities, which may prevent the classical picture of peritonitis.[17,22,26] We observed other rare types of infections, each one of the cases with enteric fever, pulmonary tuberculosis and meningitis in this study which is also consistent with other studies.[7,8, 23]

A high index of suspicion regarding infection should be kept while evaluating the children with new onset of nephrotic syndrome. A long term multicenter study on spectrum of infections in nephrotic children is recommended.

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